REMARKS

Claims 1-4, 6, 9-12, 14, and 23-26 are pending in this application. By this amendment claims 1 and 6 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification. In particular, support for the amendment to claim 1 is found at least at page 13, lines 25 through page 14, lines 1-3; and page 37, lines 21-25. Thus, claims 1-4, 6, 9-12, 14, and 23-26 are under consideration in this application. The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future related application(s).

Drawings Objection

Pursuant to the Notice of Draftperson's Patent Drawing Review, new drawings in compliance with 37 C.F.R. 1.121(d) and 1.84 are submitted herewith as Replacement Sheets.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-4, 6, 23, and 24 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner alleges that it is unclear how an ISS can both delay the development of a lesion and be administered to the cite of a lesion. The Examiner alleges that the claims therefore exclude embodiments wherein the initial appearance of a lesion is deferred, slowed, retarded or postponed. Applicants disagree with the Examiners characterization of the claims and believe that the claims are sufficiently definite when considered in view of the specification and the understanding of those of skill in the art. Without acquiescing to the rejection and in an attempt to

expedite prosecution of the present application, Applicants have amended claim 1 to recite that the composition is administered at a site of exposure to papillomavirus, thereby obviating this rejection of claims.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under Section 112, second paragraph.

Rejections under 35 U.S.C. §112, first paragraph

Applicants acknowledge that the Section 112, first paragraph (enablement) rejection of claims 1-4, 6, 23, and 24 is withdrawn by the Examiner. Applicants acknowledge that the Section 112, first paragraph (written description) rejection of claims 1-4, 6, 9-12, 14, and 23-26 is withdrawn by the Examiner.

Rejection under 35 U.S.C. §103

Claims 1-4, 6, 9-12, 14, and 23-26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Beutner *et al.* (1998, *J. Am. Acad. Dermatol.* 38: 230-239 "Beutner"), Bauman *et al.* (1996, *Pediatr. Clin. N. Am.* 48(6): 1385-1401 "Bauman"), and Yamamoto *et al.* (1994, *Jpn. J. Cancer Res.* 85: 775-779 "Yamamoto"), and further in view of Raz *et al.* (U.S. Patent 6,514,948 "Raz") and Schwartz *et al.* (WO 98/55495 "Schwartz"). Applicants respectfully traverse this rejection.

Applicants do not agree or concede that a *prima facie* case of obviousness has been established and submit that the invention is non-obvious in view of the cited references. In order to establish a *prima facie* case of obviousness, there has to be, *inter alia*, some motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine reference teachings. Applicants submit that there is no motivation to combine references and, even if combined, the combination of references does not provide a reasonable expectation of successfully arriving at the claimed invention and does not teach or suggest the claimed invention.

Neither Beutner nor Bauman teach or suggest the use of an ISS, much less an ISS for delaying the development of or reducing the severity of a lesion associated with papillomavirus infection. In the Office Action mailed June 14, 2004, at page 8, the Examiner states that neither of these references teach or suggest the use of an ISS as an adjuvant.[1] Beutner is generally directed toward treatment of genital warts and in particular to the study of topically applied imiquimod (which is stated to be an inducer of IFN-α and a variety of cytokines) for the treatment of genital warts. In Beutner, the study design required that only clinically visible warts were evaluated. See Beutner page 231 under the Materials and Methods section. Bauman is generally directed to recurrent respiratory papillomatosis (RRP) and generally discusses the use of a variety of adjuvant therapies, including IFN-α. See Bauman, page 1393 under the Adjuvant Therapy section. In Beutner, any treatment of genital warts is administered after clinically visible warts are identified. In Bauman, any treatment of RRP is administered after identification of RRP.

Yamamoto generally teach that certain synthetic oligonucleotides stimulate Interferon-α. –β, and –γ production. See Yamamoto at page 775, left column. Yamamoto discloses that a variety of 45-mer oligoDNAs, the sequence of which were randomly selected from the known cDNA sequences of proteins, such as for example, 64 kDa heat shock protein, were assessed for their biological activities and were shown to stimulate murine spleen cells to produce IFN-α, -β, and γ. Yamamoto do not teach or suggest the use of a composition comprising immunostimulatory oligonucleotides for delaying the development of a lesion or reducing the severity of a lesion associated with papillomavirus infection, much less the use of a composition comprising a polynucleotide as claimed.

Raz generally relate to methods for enhancing an immune response to a substance. Raz have no suggestions of the claimed invention which recites, in part, methods for delaying development of a lesion associated with papillomavirus infection wherein said composition is administered at a site of exposure to papillomavirus and methods for reducing severity of a lesion associated with papillomavirus wherein a composition comprising an ISS is administered at a

[1] Applicants note that the claims recite that the papillomavirus antigen is not administered in conjunction with administration of the composition which comprises a polynucleotide comprising an ISS.

papillomavirus-associated lesion. Furthermore, Raz col. 1, lines 45-54 teach administration of an ISS to the subject at least one hour prior to exposure to the substance, which Raz refers to as "pre-priming" of the subject with ISS. Claim 1 recites, in part, that said composition is administered at a site of exposure to papillomavirus and claim 9 recites, in part, that said composition is administered at a lesion. By teaching methods wherein the ISS is administered prior to exposure to the substance, as a "pre-priming", Raz is teaching a different timing for administration of an ISS than the claimed invention and a different timing for administration than Beutner and Bauman. If Raz teach a different timing for administration of an ISS than Beutner and Bauman, one of skill in the art would not be motivated to combine Raz with Beutner, Bauman and Yamamoto. The Examiner has previously withdrawn a Section 103 rejection of claims in view of Beutner, Bauman and Yamamoto. See Office Action mailed December 16, 2004, page 5.

Furthermore, in applying the Section 103 rejection of claims at page 5 of the Office Action, the Examiner admits that the actual methods of the references, Raz and Beutner and Bauman, cannot be combined, states that the methodology of Raz differs from that of other references, yet the Examiner maintains the Section 103 rejection of instant claims in view of this combination. Applicants submit that since the actual methods of the references can not be combined and since the methodology of Raz differs from Beutner and Bauman, as the Examiner states, one of skill in the art would not be motivated to combine these references, and this rejection may be withdrawn on this ground.

Additionally, the Examiner makes what appears to be an erroneous statement regarding the teachings of Beutner and Bauman. The Examiner states at page 5 of the Office Action that the teaching of all three references are concerned with the use of ISS molecules for the treatment of infections. Applicants submit that neither Beutner nor Bauman teach or suggest the use of an ISS (as is acknowledged by the Examiner in the Office Action mailed June 14, 2004), much less teach or suggest the use of an ISS for delaying the development of or reducing the severity of lesions associated with papillomavirus infection.

The Examiner states at page 5 of the Office Action that the teachings of the three references (Raz, Beutner and Bauman) relate to the same class of compounds, and thus deal with the same art. Raz teach administration of an ISS to a subject at least one hour prior to exposure to a substance. Beutner relates to the study of topically applied imiquimod (which Beutner states induces a variety of cytokines including IFN-α, TNF-α, and IL-6) for the treatment of genital warts. Bauman is generally directed to recurrent respiratory papillomatosis (RRP) and generally discusses the use of a variety of adjuvant therapies, including, among others, IFN-α. Applicants request clarity from the Examiner as to which class of compounds and/or art he refers as containing all of ISS (a polynucleotide), imiquimod (a non-nucleoside hetero-cyclic amine, see Beutner at page 231) and IFN-α (a cytokine). The Examiner further alleges that the adjuvants used in the references, that is, ISS, imiquimod and IFN-α, are functional equivalents, yet provides no evidentiary basis to support this allegation. The Examiner alleges that the ISS molecule of the Raz reference would be equally useful in the method of Beutner and Bauman, yet provides no evidentiary basis to support this allegation. The cited references themselves do not support the equivalence of ISS, imiquimod and IFN-α, or the substitution of one substance for another, as the references assign a variety of activities to each of the substances. For example, imiquimod is stated by Beutner as inducing a variety of cytokines, such as TNF-α and IL-6, in addition to IFN-α. Yamamoto states that the oligoDNAs stimulated murine spleen cells to produce a variety of interferons, including interferon-α. –β, and –γ. The Examiner must provide some evidentiary basis for the scientific principles he relies on in maintaining the argument that ISS, imiquimod and IFN-α, are functional equivalents.

In view of the above, Applicants submit that there would be no motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine the Raz and Beutner and Bauman reference teachings. Yamamoto, which disclose the use of oligoDNAs, have no teachings or suggestions regarding lesions associated with papillomavirus infection, and do not cure the deficiencies of the Raz and Beutner and Bauman combined reference teachings. Even if these references were properly combined, which Applicants don't concede, the combination does not teach or suggest all the

limitations of the claimed invention and does not provide a reasonable expectation of successfully arriving at the claimed invention.

Schwartz have no suggestions of the claimed invention which recites, in part, methods for delaying development of a lesion associated with papillomavirus infection wherein a composition comprising an ISS is administered at a site of exposure to papillomavirus and methods for reducing severity of a lesion associated with papillomavirus wherein a composition comprising an ISS is administered at a papillomavirus-associated lesion. The Examiner alleges that the cytokine induction properties of the ISS are recognized in the Schwartz reference at pages 4 and 29. Schwartz in the Background section at page 4 state that the presence of an ISS in an antigen-encoding plasmid vector injected intradermally prompted the production of large amounts of IFN-α, IFN-β, and IL-12. Schwartz at page 29 state that the phosphorothioate oligonucleotides 1, 2 and 7 are stimulators of secretion of IL-12, IFN-γ, and IL-6. These sections of Schwartz do not teach or suggest that administration of an ISS-containing polynucleotide without antigen results in the production of IFN-α. Schwartz does not cure the deficiencies of Beutner and Bauman and Yamamoto. Applicants submit that there would be no motivation or suggestion provided by the references, or in combination with the knowledge available to the skilled artisan, to modify the art cited or to combine Schwartz, Beutner and Bauman and Yamamoto reference teachings. Even if these references were properly combined, which Applicants don't concede, the combination does not teach or suggest all the limitations of the claimed invention and does not provide a reasonable expectation of successfully arriving at the claimed invention.

In view of the above, Applicants request reconsideration and withdrawal of the rejections of claims under Section 103.

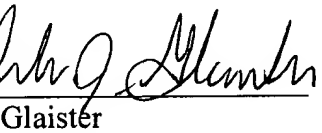
CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 7, 2005

Respectfully submitted,

By 

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Attachments